EXHIBIT B

**TO THE DECLARATION
OF DIANE C. RAGOSA, ESQ. IN
SUPPORT OF DEFENDANTS' MOTION FOR
PARTIAL SUMMARY JUDGMENT OF ANTICIPATION
OF CLAIMS 1, 2 AND 5 OF U.S. PATENT NO. 7,662,787**

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SHIRE LLC, et al., Plaintiffs, v. AMNEAL PHARMACEUTICALS, LLC, et al., Defendants.	C.A. No. 2:11-cv-03781(SRC)(CLW) (CONSOLIDATED)
SHIRE LLC, et al., Plaintiffs, v. WATSON LABORATORIES, INC. et al., Defendants	C.A. No. 2:12-cv-00083-SRC-CLW

EXPERT REPORT OF GREGORY C. FU
CONCERNING ANTICIPATION

TABLE OF CONTENTS

My name is Gregory C. Fu. I have been engaged as a technical expert by counsel for Defendants to study and provide my opinions in connection with this case. My time in this effort is being compensated at my customary rate of $625 per hour and $1250 per hour for testimony at deposition or trial. My compensation does not depend upon the ultimate outcome of this case. My CV appears as Exhibit 1 and includes a list of cases in which I have testified as an expert in the past four years.

I. PROFESSIONAL AND EDUCATIONAL BACKGROUND

1. I received a Bachelor of Science degree in Chemistry from the Massachusetts Institute of Technology (MIT) in 1985, having worked in the laboratory of Professor K. Barry Sharpless. I worked in the laboratory of Professor David A. Evans at Harvard University and received a Ph.D. degree in Organic Chemistry in 1991. I undertook postdoctoral studies in the laboratory of Professor Robert H. Grubbs at the California Institute of Technology from 1991-1993.

2. From 1993 to 2012, I was a faculty member at MIT. I was promoted from assistant professor of chemistry (1993) to the Firmenich Professor of Chemistry (2007).

3. I am currently the Altair Professor of Chemistry at the California Institute of Technology.

4. I have received a number of awards and recognitions over the years, including the Corey Award of the American Chemical Society, the Award for Creative Work in Synthetic Organic Chemistry of the American Chemical Society, and the Mukaiyama Award of the Society of Synthetic Organic Chemistry of Japan, as well as election as a fellow of the American Academy of Arts and Sciences and the Royal Society of Chemistry.

5. Throughout the past twenty years, my research has focused on the area of organic chemistry, primarily the synthesis of new and existing organic compounds, including, in some

instances, new compounds that exhibit therapeutic efficacy. Synthetic methods that I investigate are directed at the discovery of more efficient routes to the synthesis of target molecules, as well as enabling the synthesis of molecules that have not previously been made. My laboratory has synthesized thousands of compounds over the years. One area of particular emphasis is enantioselective synthesis.

6. An example of our efforts in this area is the development of the first method for the direct catalytic enantioselective synthesis of aza-β-lactams from achiral precursors. We contributed some of these new compounds to the Molecular Libraries Program of the National Institutes of Health, and this led to collaborations with scientists at The Scripps Research Institute and the Ludwig-Maximilians-Universität in Munich revolving around the therapeutic efficacy of the aza-β-lactams. In addition, medicinal chemists and biologists elsewhere, including Yale University, Princeton University, and Novartis, have taken an interest in these compounds.

7. My laboratory also has a long-standing interest in amino acids (including protected and deprotected amino acids), and I have authored several publications in the area. Furthermore, I have extensive experience employing protecting groups in synthetic reactions, as well as removing them through deprotection reactions.

II. INTRODUCTION AND SUMMARY OF OPINIONS

8. I have been retained as an expert witness by Defendants Actavis Elizabeth LLC and Actavis, LLC, Amneal Pharmaceuticals, LLC, Johnson Matthey Inc. and Johnson Matthey Pharmaceutical Materials, Mylan Pharmaceuticals Inc. and Mylan Inc., Roxane Laboratories, Inc. and Sandoz Inc. (collectively "Defendants") in the above matter. If called to testify at trial in this matter, I may testify with regard to the opinions and bases set forth below.

9. I am told there are 18 patents in this matter, including U.S. Patent Nos. 7,105,486 ("the '486 patent"), 7,223,735 ("the '735 patent"), 7,655,630 ("the '630 patent"), 7,659,253 ("the '253 patent"), 7,659,254 ("the '254 patent"), 7,662,787 ("the '787 patent"), 7,662,788 ("the '788 patent"), 7,671,030 ("the '030 patent"), 7,671,031 ("the '031 patent"), 7,674,774 ("the '774 patent"), 7,678,770 ("the '770 patent"), 7,678,771 ("the '771 patent"), 7,687,466 ("the '466 patent"), 7,687,467 ("the '467 patent"), 7,700,561 ("the '561 patent"), 7,718,619 ("the '619 patent"), 7,723,305 ("the '305 patent"), and 7,713,936 ("the '936 patent") (collectively, the "Patents in-suit").

10. Although I have reviewed all 18 Patents in-suit, I have been asked by counsel for Defendants to focus my opinions on claims 1 and 2 of the '787 patent as they pertain to the claim element "isolated L-lysine-d-amphetamine." My opinions extend to all other claims in the Patents in-suit that require the presence of this claim element.

11. Briefly, for the reasons set forth below, it is my opinion that:

- AU 54,168/65 to Hellerbach et al. ("Hellerbach") discloses and anticipates "isolated L-lysine-d-amphetamine" and "L-lysine-d-amphetamine," as recited by claims 1 and 2 of the '787 patent and the claims of the other Patents in-suit. First, Hellerbach discloses N^{α}-tosyl-L-lysine-d-amphetamine with guidance to deprotect it, which provides isolated L-lysine-d-amphetamine, as construed by the parties and the Court. Second, Hellerbach specifically discloses a small genus of amino acid-conjugated d-amphetamine compounds such that one of ordinary skill can immediately envision each species of the genus, including isolated L-lysine-d-amphetamine.

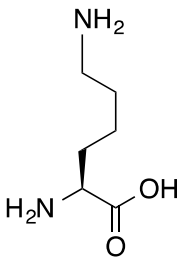
- Although my opinions above focus on the above-referenced claims in the '787 patent, they also apply to any claim in the Patents in-suit reciting "L-lysine-d-amphetamine."

12. In providing my opinions herein, I have considered a number of documents, which I have listed in Exhibit 2. This Report is based on information known to me as of the date of my signature, and I reserve the right to amend or supplement it based on further preparation or discovery in this action, including my review of any further expert statements or reports submitted on behalf of Plaintiffs. I reserve the right to supplement or amend my opinions in response to opinions expressed by Plaintiffs' experts, or in light of any additional evidence, testimony, or other information that may be provided to me after the date of this Report, including at trial. In addition, I expect that I may be asked to testify in rebuttal to issues that may be raised in the reports of Plaintiffs' experts, or to issues that may be raised by fact witnesses and technical experts at trial.

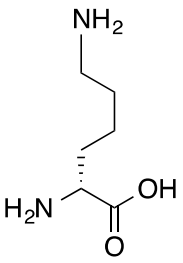
III. SCIENTIFIC AND TECHNICAL BACKGROUND

13. This Report concerns the chemical compound L-lysine-d-amphetamine. L-lysine-d-amphetamine includes the combination of L-lysine and d-amphetamine. Each of L-Lysine and d-amphetamine is one member of a pair of enantiomers.

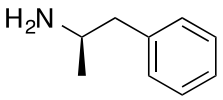
14. Enantiomers are mirror images of one other, and they are analogous to otherwise identical left-handed and right-handed gloves. Thus, although enantiomers have the same number and kinds of atoms that are connected in the same order, they cannot be superimposed, just like a left-handed glove cannot be superimposed onto a right-handed glove. One of the naming conventions used to describe these different configurations is the "L" configuration and the "D" configuration, or simply the L and D enantiomers. Another naming convention uses lower case l and d to describe the different enantiomers. For example, the L and d enantiomers of lysine and amphetamine are shown below:



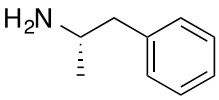
L-lysine



D-lysine



l-amphetamine



d-amphetamine

The bolded lines signify that the group of atoms is projecting toward the reader and out of the page, whereas the dashed lines signify that the group of atoms is projecting away from the reader and into the page.

15. L-lysine is an optically active α-amino carboxylic acid that can be obtained from proteins. Amino acids, including α-amino acids, contain amine (-NH_2 and related) and carboxylic acid (-COOH) groups. L-Lysine (shown above) is one of a small group of amino acids derived from proteins.

16. Attaching amino acids, like L-lysine, to d-amphetamine involves straightforward reaction chemistry to one of ordinary skill in the art. The chemistry involves forming an amide bond between the amino acid (*e.g.*, L-lysine) and d-amphetamine. The amide bond is formed by reacting a derivative of the carboxylic acid moiety (-COOH) of the amino acid with the amino moiety (-NH_2) of d-amphetamine to form the amide (-CONH-) that links the two molecules into one. Because amino acids have not only a carboxylic acid moiety (-COOH), but also at least one amino moiety, the amino group(s) of the amino acid can be blocked (*i.e.*, protected), in order to ensure that it does not react with the carboxylic acid derivative.

17. Thus, when conjugating L-lysine to d-amphetamine, protection of the amino moieties of the L-lysine avoids unwanted side reactions between these amino groups and the carboxyl group of the L-lysine. The desired reaction between the amine group of d-amphetamine and the carboxyl group of L-lysine can then occur, forming a protected L-lysine-d-amphetamine conjugate. Prior to the filing of the Patents in-suit, different types of protecting groups were known to those of skill. Hellerbach at page 8, for example, discloses carbobenzoxy, tosyl, formyl, benzyl, dibenzyl, phthalyl, trifluoroacetyl, and nitro protecting groups.

18. Deprotection reactions, to remove these protecting groups after the desired reaction, such as between the amino acid and the active drug substance, were also well-known before the filing of the Patents in-suit. (Hellerbach at 14 and Examples 2 and 9.) Such deprotection reactions are extremely common in the field of organic synthesis.

IV. PATENTS IN-SUIT

19. I have reviewed all 18 Patents in-suit and their file histories. Although my focus is the '787 patent, I will also summarize the file histories of other Patents in-suit.

20. I am told that Shire asserts that many of the Patents in-suit are entitled to the benefit of the filing date of certain provisional applications. Those provisional applications include U.S. Provisional App. No. 60/473,929 and U.S. Provisional App. No. 60/567,801 ("the '929 and '801 applications"), which were filed on May 29, 2003 and May 5, 2004. For the purposes of my analysis, I have assumed that claims 1 and 2 of the '787 patent and all other claims reciting the compound L-lysine-d-amphetamine are entitled to a filing date of May 29, 2003.

A. Patent Claims

Claims 1 and 2 of the '787 patent recite:

1. A compound selected from the group consisting of isolated L-lysine-d-amphetamine and a pharmaceutically acceptable salt of L-lysine-d-amphetamine.

2. Isolated L-lysine d-amphetamine.

('787 patent at col. 62, ll 20-28.)

B. The Specifications

21. The specifications of the Patents in-suit are extensive. They are similar with certain differences in their disclosures relating to L-lysine-d-amphetamine.

22. Example 2 of the '787 patent discloses how to make the hydrochloride salt of L-lysine-d-amphetamine. ('787 patent at col. 20, l 40-col. 21, l 32.) During the initial coupling step, Boc-Lys(Boc)-OSu, which is a lysine derivative that is protected by two Boc's, is added to d-amphetamine under an inert atmosphere. (Col. 20, l. 46-col. 21, l. 8) After the coupling step yields protected L-lysine d-amphetamine, the Boc protecting groups are removed by deprotection, and the HCl salt of L-lysine-d-amphetamine is formed.

C. Prosecution Histories

23. I have reviewed the prosecution histories of the Patents in-suit. Nearly all prosecution histories include the same Reasons for Allowance, which were mailed by the Examiner around the same time. (*See, e.g.,* '630 patent at 10/6/09 NoA; '253 patent at 10/6/09 NoA; '254 patent at 10/6/09 NoA; '788 patent at 10/6/09 NoA; '030 patent at 10/6/09 NoA; '031 patent at 10/19/09 NoA; '774 patent at 10/7/09 NoA; '770 patent at 10/7/09 NoA; '771 patent at 10/6/09 NoA; '466 patent at 10/6/09 NoA; '467 at 10/6/09 NoA; '561 patent at 11/16/09 NoA; '936 patent at 10/6/09 NoA; '619 patent at 12/30/09; and '305 patent at 3/8/10 NoA.) The prosecution histories of the '735, '486, and '787 patents include different exchanges with the Patent Office that preceded most others in time, and I will discuss them separately. The '486 and

'735 patents were filed on the same day – June 1, 2004. The '787 patent was filed approximately three years later, on May 7, 2007.

1. **The Application Supporting the '486 Patent**

24. The application that led to the '486 patent, as originally filed, included 36 claims to methods and compositions comprising amphetamine covalently bound to any chemical moiety. For example, original claim 1 stated:

> 5. A method for reducing or preventing abuse of amphetamine, comprising providing to a human in need thereof a composition comprising amphetamine covalently attached to a chemical moiety, wherein the pharmacological activity of said composition is decreased when used in a manner inconsistent with the manufacturer's instructions.

Dependent claims 15-18 identified lysine, serine, phenylalanine, and glycine as chemical moeities.

25. In a series of amendments, the claims were narrowed. An amendment filed on February 16, 2006 limited all claims to methods for treating attention deficit hyperactivity disorder (ADHD) with L-lysine-d-amphetamine or salts thereof. (2/16/06 Preliminary Am.)

26. On March 13, 2006, the Patent Office mailed a Notice of Allowance, noting in Reasons for Allowance that the claims were allowed based on the recitation of the method aspects.

27. The '486 patent issued on September 12, 2006.

2. **The Application Supporting the '735 Patent**

28. As originally filed, the application that led to the '735 patent included 35 claims covering compounds, compositions, and methods of use. Claim 1 recited a "compound comprising amphetamine covalently bound to lysine." Claim 2 narrowed lysine to a single lysine.

29. On February 17, 2005, an amendment cancelled all 35 claims and added new claims 36-51. (2/17/05 Preliminary Am.) These new claims recited "L-lysine-d-amphetamine" and "A composition comprising L-lysine-d-amphetamine or salts thereof and a pharmaceutically acceptable additive in a form suitable for oral administration." (*Id.*)

30. On May 8, 2006, the Patent Office sent a non-final rejection. (5/8/06 OA.) According to the Examiner, NL 6414901 discloses protected L-lysine-d-amphetamine in the form of N^{α}-tosyl-L-lysine-d-amphetamine, and the unprotected form is an obvious variant. (*Id.* at 5-6.) In response to the rejection, Applicants, on October 10, 2006, amended all claims to require the presence of an "unprotected prodrug." (10/10/06 OA Response.)

31. On January 23, 2007, the Examiner allowed the claims. The Examiner also offered Reasons for Allowance, stating "the prior art of record is no longer deemed to reasonably teach or suggest, or provide motivation for making/using a pharmaceutical composition comprising an unprotected prodrug consisting of L-lysine-d-amphetamine."

32. The '735 patent issued on May 29, 2007.

3. **The Application Supporting the '787 Patent**

33. The application that led to the '787 patent was filed on May 7, 2007. Claim 36 recited "A compound selected from the group consisting of L-lysine-d-amphetamine and a pharmaceutically acceptable salt thereof."

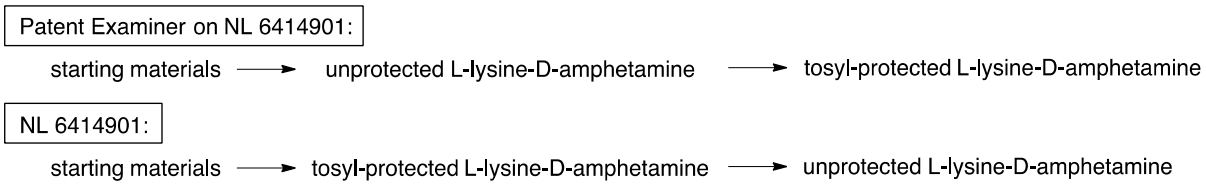
34. On November 12, 2008, the Examiner mailed a non-final rejection that included essentially the same grounds and arguments as the May 8, 2006 rejection in the '735 patent (*i.e.*, that the claims covered obvious variants of N^{α}-tosyl-L-lysine-d-amphetamine as disclosed in NL 6414901). (11/12/08 OA.) In their May 12, 2009 response, Applicants argued that "the only amphetamine derivatives that are expressly characterized as "active" compounds in NL '901 are protected forms of amino acid—amphetamine conjugates." (5/12/09 OA Response at pages 5-6.)

35. On September 22, 2009, the Examiner allowed the claims. (9/22/09 Notice of Allowance.) With respect to claims 1 and 2, the Examiner required the Applicants to insert the word "isolated" before L-lysine-d-amphetamine. (*Id.* at 2.) The Examiner also provided Reasons for Allowance, which state:

> The prior art of record (NL 6414901), drawn to a protected L-Lys-d-amphetamine-Tosyl, was determined to be a prodrug of the presently claimed UNprotected L-Lys-d-amphetamine. The art of record only teaches/suggests that a protected form of the compound could be administered and have utility/enablement for a therapeutic use. Counterintuitively, Applicant has provided by description and declaration unexpected results showing that the unprotected form carries out the intent of the invention. Thus, an intermediate of the protected end product of '901 not being described as an end product itself (what the present invention is in essence, an intermediate), there would have been no suggestion/motivation/predictability in the '901 alone or in combination, for one of ordinary skill in the art to have arrived at the presently claimed UNprotected, intermediate form thereof.

('787 9/22/09 Reasons for Allowance at 2-3.)

36. In the Reasons for Allowance, the Examiner appears to have misunderstood NL 6414901. Unprotected L-lysine-d-amphetamine is **not** an intermediate in the synthesis of protected L-lysine-d-amphetamine, as the Examiner states. In fact, one of ordinary skill would understand that NL 6414901teaches the opposite: that protected L-lysine-d-amphetamine is an intermediate in the synthesis of unprotected L-lysine-d-amphetamine.



37. On October 1, 2009, Applicants filed Comments on Statement of Reasons for Allowance. (10/1/09 Comments.) Among other things, the Applicants stated that NL 6414901 "does not specifically describe the synthesis of N^{α}-tosyl-L-lysine [D(+)-1-phenyl-propyl-2]-amide" or its unprotected form and that "there is no evidence of record that N^{α}-tosyl-L-lysine

[D(+)-1-phenyl-propyl-2]-amide is an intermediate form of L-lys-d-amphetamine or vice versa." (*Id.* at 2.) A person of ordinary skill would understand that NL 6414901 is teaching that N^{α}-tosyl-L-lysine-d-amphetamine (protected L-lysine-d-amphetamine) would serve as an intermediate in the synthesis of unprotected L-lysine-d-amphetamine. (*See* NL 6414901 at 1 and 4.)

38. The '787 patent issued on February 16, 2010.

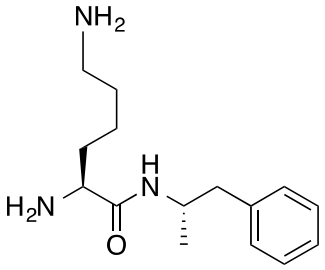
4. **The Applications Supporting the Remaining Patents in-suit**

39. As mentioned above, the applications leading to the remaining Patents in-suit have similar prosecutions, and their Notices of Allowance include essentially the same Reasons for Allowance as the '787 patent.

40. I do not agree with the Examiner's conclusions for the reasons set forth below. I also note that the Examiner did not focus on the Australian counterpart of NL 6414901 (*i.e.*, Hellerbach), which includes significantly more disclosure than NL 6414901. Furthermore, the Examiner misinterpreted NL 6414901.

V. CLAIM CONSTRUCTION

41. Counsel has advised me that the meaning of certain claim terms may relate to my opinions. I am told that the parties have agreed to the meaning of the term "isolated," as recited by claim 2 of the '787 patent. I am told the agreed upon definition is "a substance separated from a crude mixture of reactants and/or solvents." In addition, I understand the Court issued a Claim Construction Order on August 8, 2013, where it defined the meanings of certain terms. (Claim Construction Order.) I am told the Court construed the term L-lysine-d-amphetamine to mean:



L-lysine-d-amphetamine

This is the unprotected form of the compound. In reaching my opinions concerning anticipation, I have considered the above definitions and applied them in my analysis.

VI. PERSON OF ORDINARY SKILL IN THE ART

42. As advised by counsel, the Patents in-suit encompass many aspects of pharmaceutical science, including drug development, organic chemistry, pharmacokinetics, pharmaceutical formulation, X-ray crystallography, and medicine.

43. As such, the person of ordinary skill in the art would be a team of individuals who had, as of May 29, 2003, a high level of education and skill, including an M.D. or a Ph.D. and two years of work experience in the appropriate field, or alternatively, a Bachelor's or Master's Degree and a commensurately greater number of years of experience in the appropriate field. Each of the individuals in the team constituting the person of ordinary skill in the relevant art would have a working knowledge of one or more of the interdisciplinary fields of pharmaceutical drug product development, organic chemistry, analytical chemistry, pharmacokinetics, pharmaceutical formulation, X-ray crystallography, medicine, and any other related field.

44. I am told that Shire defines one of ordinary skill as a person with an academic degree of Doctor of Philosophy (or equivalent degree) in a field related to pharmaceutical sciences with approximately 1 year of relevant experience, or alternatively, a person with commensurate experience.

45. I have rendered my opinions herein are from the perspective of one of ordinary skill in the art.

VII. ANALYSIS

46. It is my opinion that the prior art anticipates "isolated L-lysine-d-amphetamine" as construed by the parties and the Court, and as recited by claims 1 and 2 of the '787 patent. These opinions also apply to any claim in the Patents in-suit reciting "L-lysine-d-amphetamine," including, for example, claims 1, 15 and 18 of the '735 patent, which characterize L-lysine-d-amphetamine as an "unprotected prodrug." Unprotected L-lysine-d-amphetamine is a prodrug, defined as a molecule metabolized in the body into an active pharmaceutical compound.

47. I have been told that I must take certain legal principles into account in reaching my opinions. I am told patents are presumed valid. I am further told that Defendants bear the burden of proving invalidity by clear and convincing evidence. I am informed that this clear and convincing evidence standard means Defendants must show invalidity is substantially more probable than not. I have taken these principles into account when forming my opinions in this case.

48. I am also informed that anticipation requires an express or inherent disclosure in a single prior art reference of all elements of the claim under consideration, arranged as in the claim. I understand that identity of terminology is not required. I further understand that when a prior art reference discloses a genus of compounds without identifying individual species and the claim under consideration recites one of those individual species, there is nonetheless anticipation if one of ordinary skill would immediately envisage each species of the genus. I further understand that anticipation requires that the single reference inform one of skill in the art how to make and use the invention without undue experimentation.

49. It is my opinion that Hellerbach is just such a single prior art reference and that one of ordinary skill would understand it to disclose isolated L-lysine-d-amphetamine under the parties' and the Court's constructions related to this term. Thus, Hellerbach anticipates claims 1 and 2 of the '787 patent.

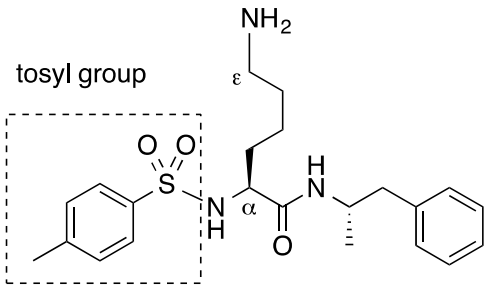
50. Hellerbach provides two separate anticipating disclosures. First, Hellerbach discloses N^{α}-tosyl-L-lysine-d-amphetamine with instructions that would yield "isolated L-lysine-d-amphetamine." Second, Hellerbach discloses a small genus of amino acid-conjugated d-amphetamine compounds from which one of ordinary skill can immediately envision each species of the genus, including "isolated L-lysine-d-amphetamine."

A. Deprotected N^{α}-tosyl-L-lysine-d-amphetamine

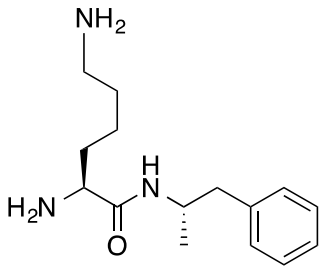
51. Hellerbach anticipates isolated L-lysine-d-amphetamine through its disclosure of a protected form of the molecule, along with instructions to deprotect it. The deprotected molecule is L-lysine-d-amphetamine, as construed by the Court and as recited by claims 1 and 2 of the '787 patent.

52. Hellerbach, starting at page 27 and ending at page 29, discloses a table of "compounds included within the purview of the present invention." This table classifies its compounds as "Amide of Formula I."

53. Example 24 in this table, at page 29, is protected L-lysine-d-amphetamine. Specifically, the compound in Example 24 is N^{α}-tosyl-L-lysine [D(+)-1-phenyl-propyl-(2)]-amide (*i.e.*, N^{α}-tosyl-L-lysine-d-amphetamine), which has the illustrated chemical structure:



Nα-tosyl-L-lysine-d-amphetamine



L-lysine-d-amphetamine

As shown, N^{α}-tosyl-L-lysine-d-amphetamine includes a tosyl protecting group positioned on the α-amino group of the L-lysine portion of the molecule.

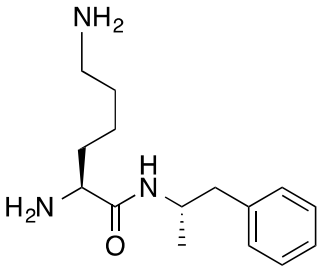
54. As indicated in the table heading, this compound – N^{α}-tosyl-L-lysine [D(+)-1-phenyl-propyl-(2)]-amide – is an "Amide of Formula I":

Example	Amide of Formula I	Melting Point	$(\alpha)_D^{23}$	Manufactured according to the procedures of Example
24	N^{α}-Tosyl-L-lysine [D(+)-1-phenyl-propyl-(2)]-amide	224-225°C	+ 31.8° (c = 1- in 95% acetic acid)	3

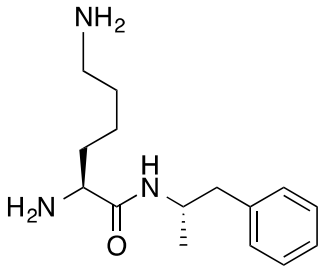
(Hellerbach at 29.)

55. Hellerbach's disclosure also expressly directs one of ordinary skill to remove the protecting groups from the α amino groups of these conjugates. For example, at page 7, Hellerbach states "the amide so formed may be treated by conventional procedures to split off the protecting means whereby to produce a compound of formula I above having a free α-amino group." Likewise, at page 8, Hellerbach states "the protecting group should be such that . . . if desired, it be readily removed from compounds of formula I above by conventional techniques." Finally, at page 14, Hellerbach states, "[a]ny of the groups which protect the α-amino function…may be cleaved from the end product amides of formula I above by any convenient technique."

56. When one of ordinary skill follows the teachings of Hellerbach to deprotect amides of Formula I at their α-amino groups, the compound illustrated in Example 24, through removal of its tosyl group, corresponds exactly to "isolated L-lysine d-amphetamine" under the parties' and the Court's constructions:



the product of deprotection of the tosyl group of Nα-tosyl-L-lysine-d-amphetamine



L-lysine-d-amphetamine

Thus, because Hellerbach discloses that protecting groups can be cleaved from the protected amides (Hellerbach at 7, 8 and 14) and because various unprotected compounds appear in the table as final products (Hellerbach at Examples 15, 17, 19 and 21; see also Example 1), Hellerbach has taught the synthesis of isolated L-lysine-d-amphetamine.

57. Indeed, page 14 of Hellerbach notes that a "tosyl group can be removed by the treatment of a so-substituted amide of formula I above with sodium in liquid ammonia." The only tosyl-protected conjugate that is specifically described in Hellerbach is N^{α}-tosyl-L-lysine-d-amphetamine.

58. By connecting the deprotecting disclosures on pages 7, 8, and 14 with the "Amide of Formula I" described in Example 24 of the table that spans pages 27-29, one arrives at isolated L-lysine d-amphetamine, as construed by the parties and the Court and as recited by claims 1 and 2 of the '787 patent and all other claims of the Patents in-suit. As shown above, the Court's construction of L-lysine-d-amphetamine is identical to the deprotected form of the compound in Example 24 of Hellerbach.

59. Further, one of ordinary skill in the art could employ the teachings of Hellerbach to make the amide in Example 24 and isolate its deprotected form, L-lysine-d-amphetamine. According to the table that spans pages 27-29, N^{α}-tosyl-L-lysine [D(+)-1-phenyl-propyl-(2)]amide is "Manufactured according to the procedures of Example 3." The coupling reaction employed there is described more generally at pages 11-14 – reaction A. In addition, Hellerbach discloses various deprotection reactions. At page 14, Hellerbach provides a method for the removal of tosyl protecting groups - with sodium in liquid ammonia. This is a standard reaction well-known in the field. These disclosures would enable one of ordinary skill to readily synthesize and isolate unprotected L-lysine-d-amphetamine.

60. Because Hellerbach makes clear that protected L-lysine-d-amphetamine is an intermediate in the synthesis of unprotected L-lysine-d-amphetamine, the unprotected form of the compound is the end product. In other words, once the deprotection reactions disclosed in Hellerbach run their course on N-tosyl protected L-lysine-d-amphetamine, unprotected L-lysine-d-amphetamine is the isolated end product. (Hellerbach at 7, 8 & 14.) Further, various examples in Hellerbach disclose unprotected L-series amino acid conjugates of d-amphetamine as isolated end products. (Hellerbach at Examples 15, 17, 19 and 21.)

61. I recognize that during prosecution of the '787 patent, the patentee overcame the Examiner's rejection based upon NL 6414901, which is a counterpart to Hellerbach. As I mentioned above in Section 3, the Examiner who reviewed the '787 patent misunderstood NL 6414901. The Examiner mistakenly believed that unprotected L-lysine-d-amphetamine was an intermediate in the synthesis of N^{α}-tosyl-L-lysine-d-amphetamine, which prompted the introduction of the "isolated" claim language. In fact, NL 6414901 teaches that unprotected L-

lysine-d-amphetamine would be isolated from N^{α}-tosyl-L-lysine-d-amphetamine, not the other way around. (NL 6414901 at 4.)

62. I further note that NL 6414901 includes far less disclosure than Hellerbach. Unlike Hellerbach, NL 6414901 does not expressly connect the removal of protecting groups to an "amide of formula I" (illustrated in Hellerbach), the table on pages 10-11 of NL 6414901 does not identify N^{α}-tosyl-L-lysine [D(+)-1phenylpropyl-2]-amide as an "Amide of Formula I", and the discussion of the deprotection of a tosyl group does not refer to an "amide of formula 1." Hellerbach clearly teaches the reader about the synthesis of unprotected amino acid–amphetamine conjugates, including L-lysine-d-amphetamine, from protected precursors.

B. Genus/species

63. Hellerbach also anticipates L-lysine-d-amphetamine in a second way. Two preferred subgenera within Hellerbach would allow one of ordinary skill to immediately envision small groups of specific compounds, including unprotected L-lysine-d-amphetamine. First, a preferred subgenus of Formula II specifies 18 particular unprotected amino acid conjugates of d-amphetamine, including L-lysine-d-amphetamine. Second, a preferred subgenus of Formula IV (section a) specifies 17 particular unprotected amino acid conjugates of d-amphetamine, including unprotected L-lysine-d-amphetamine.

64. There are various chemical formulas in Hellerbach. I will focus on Formulas I-IV, which are relevant to my opinions in this Report. Formula I describes amphetamine conjugated to optically active α-amino carboxylic acids, wherein the α-amino group may be free or protected. Formulas II and III separate Formula I into the free and the protected species, respectively, with Formula III providing the further condition that the protecting group be "readily removable therefrom by conventional means." This latter requirement of ready

removability makes clear the high interest of Hellerbach in synthesizing deprotected amino acid–amphetamine conjugates. This interest is reinforced in other sections of the patent, e.g., "The invention is further characterized in that the amide so-formed may be treated by conventional procedures to split off the protecting means whereby to produce a compound of formula I above having a free α-amino group." (Hellerbach at 7)

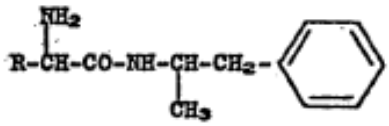
65. Hellerbach narrows the preferred subgenus of Formulas I–IV in other ways. Although none of the formulas indicate specific enantiomeric forms, other disclosures identify d-amphetamine and the L-series of amino acids as preferred. According to pages 7-8, "the use of optically pure D(+)-amphetamine . . . is preferred" (*i.e.*, d-amphetamine). With respect to the amino acid, Hellerbach states on page 7 that "Acids of the L-series are preferred since the use thereof generally results in end products which are of greater value, in a therapeutic sense".

66. Formula IV (section a), on page 4 in Hellerbach, identifies 17 specific unprotected conjugates of amphetamine with optically active α-amino carboxylic acids "having a free α-amino group." In particular, Formula IV (section a) identifies the following optically active α-amino carboxylic acids: "alanine, valine, leucine, isoleucine, proline, serine, threonine, **lysine**, arginine, histidine, phenylalanine, tyrosine, tryptophane, cysteine, methionine, glutamic acid, and aspartic acid".

(Emphasis mine.) Thus, one of the 17 compounds is isolated L-lysine-d-amphetamine.

67. Formula II at page 2 in Hellerbach also discloses a genus of amino acid–amphetamine conjugates ("one group of novel compounds included within the purview of the present invention"):

Thus, one group of novel compounds included within the purview of the present invention are of the formula



II

wherein R is a residue of an optically active α-amino carboxylic acid

and acid addition salts thereof with pharmaceutically acceptable acids.

The chemical structure shown in Formula II includes two parts. First, it includes an amphetamine-derived portion, starting on the right with the ring structure and extending to the NH group. Second, it includes an amino acid-derived portion, starting with the CO group and extending left to the R group. According to Formula II, R is "a residue of an optically active α-amino carboxylic acid."

68. The illustration of Formula II and the surrounding discussion make clear that the amino acid–amphetamine conjugates of Formula II are free of a protecting group on the α-amino group (NH_2). In the illustration of Formula II, the nitrogen atom in the amino acid-derived portion of the molecule is bonded to two hydrogens, without a protecting group. Nor is there any mention in the text about a protecting group on this nitrogen.

69. Specific residues that can constitute "R" in Formula II are further defined in the surrounding disclosure of Hellerbach.

70. Based on Formula IV (section a), the "advantageous" subgenus of compounds falling under Formula II includes 17 members, including L-lysine-d-amphetamine. That is,

based on the amino acids identified in Formula IV (section a), there are 17 "advantageous" residues or side chains of amino acids.

71. Hellerbach also specifically identifies 18 preferred residues of optically active α-amino carboxylic acids at page 7, which states:

> "Optically active α-amino carboxylic acids . . . are represented, preferably, by those derived from proteins such as optically active alanine, valine, leucine, isoleucine, proline, serine, threonine, **lysine**, arginine, histidine, phenylalanine, tyrosine, tryptophane, cystine, cysteine, methionine or optically active glutamic acid, aspartic acid and the like."

(Emphasis mine.)

72. One of skill would, therefore, immediately envision all 17 or 18 specific compounds within the subgenera of unprotected L-series amino acids conjugated with d-amphetamine of Formulas II and IV. Among these species is isolated L-lysine-d-amphetamine, which one of ordinary skill would immediately envision. The compound is isolated because there is no indication in the chemical formulas that any reactants and solvents are present.

73. I note that NL 6414901, which the Patent Office applied throughout prosecution of the 18 Patents in-suit, discloses neither Formula II nor Formula IV (section a) of Hellerbach, both of which clearly disclose unprotected amino acid–amphetamine conjugates.

74. Hellerbach differs from NL 6414901 in another way. On page 6 of their May 12, 2009 Amendment in the prosecution of the '787 patent, the patentee observed that only protected amino acid–amphetamine conjugates are described in the claims of NL 6414901, suggesting that NL 6414901 does not teach **un**protected conjugates. In Hellerbach, the claims specifically cite three unprotected amino acid–amphetamine conjugates. (Claims 11, 13, and 14.)

Signed and sworn under penalty of perjury this 3rd day of October 2013:

Gregory C. Fu